Attorney Docket No.: 100725-9

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	Florian Kern
SERIAL NO.	:	09/600,564
FILED	:	November 7, 2000
FOR	:	A Method for Identifying T-Cell Stimulating Protein Fragments
ART UNIT	:	1645
EXAMINER	:	Zeman, Robert A.

DECLARATION OF DR. MICHAEL RAYMOND BETTS

1. My name is Michael Raymond Betts. I am a citizen of USA residing at 133 Broadview Rd, Springfield, Pennsylvania.

2. My educational background is in the field of immunology. I obtained the degree(s) of Ph.D. from the University of North Carolina.

3. I am head of a research unit at the University of Pennsylvania, Philadelphia, Pennsylvania. My unit is involved in the design, validation and standardization of antigen-specific flow-cytometry assays. My vitae is set forth in Exhibit I. [extra information on team/unit]

4. I am the principal author of more than X Medline indexed research articles in this field summarized in Exhibit II.

5. I have carefully studied the specification and claims in the US patent application US 09/600564, and would like to make the

following declaration.

6. The method described in the claims has become a household method in many research labs following its first publication in Nature Medicine in 1998 [Kern-F et al., T-cell epitope mapping by flow-cytometry, Nature Medicine, 1998, Aug;4(8):975-8]

7. The method is based on the short term stimulation of T lymphocytes with peptides where the T lymphocytes are contained in a cell suspension. Peptides are added for stimulation. In order to be able to stimulate the T-cells, the peptides need to be uploaded onto class-I Major Histocompatibility Complex (MHC) molecules, because this is the only way they can be recognized by T lymphocytes via the T cell receptor (TCR). Loading of the peptides onto the MHC may require shortening (clipping) of peptides by some as yet not precisely identified proteolytic mechanism. The loading of peptides, including the clipping, onto class-I MHC molecules is known to be achieved within approximately 30 minutes.

8. It is known that once T-cells are being stimulated, they start synthesizing molecules which can be used to identify such stimulation. The production of these molecules, among which are cytokines, follows different kinetics. 6 hours is known to be a time after which most cytokines can be found, in particular IFN-gamma, IL-2, and TNF. No one single time-point is optimum for all cytokines; however, such cytokines will have reached reach a point of maximum secretion at approximately 12 hours following stimulation.

9. It is also known that, approximately 16 - 20 hours following stimulation, T lymphocytes may start replicating their DNA content in preparation for a cell division.

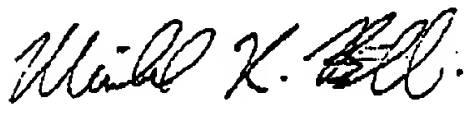
10. Typically, cell division will not occur before 24 hours after stimulation.

11. The description of the method in the claims of USSN 09/600564 states that

> ...the time of incubation [cell suspension plus peptides] should be sufficiently long so that the protein fragment or fragments are sufficiently taken up by the major histocompatibility antigen (MHC) molecules present on the cell surface, said taking up being sufficient when an unambiguous identification of stimulated T-cells is possible; and the incubation time of the suspensions containing T-cells with the protein fragment or fragments is sufficiently short so that selection and proliferation accompanied by the specific elimination of particular T-cells do not occur...
>
> The specifications further teach that this incubation time can be 6 hours.

12. In light of my explanation of what is known to those skilled in the art, the description of the method in the specification of USSN 09/600564 gives sufficient guiding to anyone skilled in the art to perform the method claimed in USSN 09/600564. Specifically, setting up the assay with a 6 hour incubation time, and then working with longer and shorter incubation times will enable everybody to make use of the method and to find the optimum incubation period for their particular system.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



12/4/2006

_Michael R. Betts , Declarant Date

EXHIBIT I

Michael Raymond Betts
Assistant Professor, University of Pennsylvania

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Maryland	B.S.	1985-1990	Zoology
University of North Carolina	Ph.D.	1992-1998	Immunology
University of Texas Southwestern Med Center		1998-2001	Immunology

Positions and Employment

1988-1989 Laboratory Technician, United States Department of Agriculture
1990-1992 Laboratory Technician, Food and Drug Administration
1992-1998 Predoctoral Fellow, University of North Carolina
1998-2001 Postdoctoral Fellow, University of Texas Southwestern Medical Center
2001-2005 Senior Research Fellow, Vaccine Research Center, National Institutes of Health
2005- Assistant Professor, Department of Microbiology, University of Pennsylvania

Other Experience and Professional Memberships

2005-2006 Member, ZRG1 AARR-C (02) Immunity and Pathogenesis in AIDS Special Emphasis Panel Study Section
2006- Member, amfAR Study Section

EXHIBIT II

Selected peer-reviewed publications (in chronological order).

1. **Betts, MR**, Krowka, J, Santamaria, C, Balsamo, K, Gao, F, Mulundu, G, Luo, C, N'Gandu, N, Sheppard, H, Hahn, BH, Allen, S, and JA Frelinger. Cross-clade Human Immunodeficiency Virus (HIV)-specific cytotoxic T-lymphocyte responses in HIV-infected Zambians. J. Virol. 71:8908-8911. 1997.
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25. Hryniewicz A, Boasso A, Edghill-Smith Y, Vaccari M, Fuchs D, Venzon D, Nacs J, **Betts MR**, Tsai WP, Heraud JM, Beer B, Blanseet D, Chougnet C, Lowy I, Shearer GM, Franchini G. CTLA-4 blockade decreases TGF-b, indolamine 2,3- dioxygenase, and viral RNA expression in tissues of SIVmac251-infected macaques. Blood. Epub online Aug 8 2006.
26. Makedonas G, **Betts MR**. Polyfunctional analysis of human T cell responses: importance in vaccine immunogenicity and natural infection. Springer Semin. Immunopathol. Epub online Aug 25 2006.

27. Casazza JP, **Betts MR**, Price DA, Precopio ML, Ruff LE, Brenchley JM, Hill BJ, Roederer M, Douek DC, Koup RA. Acquisition of direct antiviral effector functions by CMV-specific CD4+ T lymphocytes with cellular maturation. J. Exp. Med. In press.

Research Support

Ongoing Research Support
ACTIVE

K22 AI 66976-01 (Betts, Michael, PhD)
10/1/05-9/30/07
NIH
Impact of CD8+ T cell functionality on HIV escape.
The major goal of the study is to identify those functional properties of HIV-specific CTL which place immunological pressure upon the virus. This project examines the role of CD8+ T cell functionality in dictating HIV escape from immune surveillance.
Role: Principal Investigator

W.W. Smith Charitable Foundation
1/1/06-1/1/08
Modulation of HIV-specific immunity during acute and chronic infection.
The major goal of this study is to define the phenotypic and functional changes in the HIV-specific T cell repertoire that occur in clade B HIV infection. This project examines acute HIV clade B infection, HIV-specific T cell responses in chronically infected adolescents, and induced changes in HIV-specific T cell responses after therapeutic intervention.
Role: Principal Investigator

COMPLETED
Penn CFAR Developmental Grant
6/30/05-6/30/06
University of Pennsylvania Center for AIDS Research
Modulation of HIV-specific CD8+ T cell function and control of HIV replication during and after cessation of HAART.
The major goal of this study is to determine if STI can alter CD8+ T cell functionality to a more favorable protective effect. This project examines how strategic therapy interruption and extended HAART therapy influences the frequency and function of HIV specific CD8+T cells.
Role: Principal Investigator

Principal Investigator/Program Director (Last, First, Middle):

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Michael Raymond Betts	Assistant Professor, University of Pennsylvania
eRA COMMONS USER NAME MBETTS1	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Maryland	B.S.	1985-1990	Zoology
University of North Carolina	Ph.D.	1992-1998	Immunology
University of Texas Southwestern Med Center		1993-2001	Immunology

A. Positions and Honors.

Positions and Employment

1988-1989 Laboratory Technician, United States Department of Agriculture
1990-1992 Laboratory Technician, Food and Drug Administration
1992-1998 Predoctoral Fellow, University of North Carolina
1998-2001 Postdoctoral Fellow, University of Texas Southwestern Medical Center
2001-2005 Senior Research Fellow, Vaccine Research Center, National Institutes of Health
2005- Assistant Professor, Department of Microbiology, University of Pennsylvania

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2005-2006 Member, ZRG1 AARR-C (02) Immunity and Pathogenesis in AIDS Special Emphasis Panel Study Section
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